Respiratory Medicine (2010) **104**, S70–S73

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Bronchoalveolar lavage in idiopathic pulmonary fibrosis: What does it tell us?

A. Pesci [a,b,*], E. Ricchiuti [a,b], R. Ruggiero [a,b], A. De Micheli [a,b]

[a] *Dipartimento di Medicina Clinica e Prevenzione, Università degli Studi di Milano-Bicocca, Italy*
[b] *Clinica Pneumologica, Azienda Ospedaliera San Gerardo di Monza, Via Pergolesi 33 — 20052 Monza, Italy*

Available online 14 May 2010

KEYWORDS
Idiopathic pulmonary fibrosis;
Usual interstitial pneumonia;
Bronchoalveolar lavage;
Non-specific interstitial pneumonia

Summary
Bronchoalveolar lavage (BAL) has only a limited role in diagnosis of idiopathic pulmonary fibrosis (IPF). A finding of raised neutrophils (>5%) and eosinophils (>2%) is characteristic but not diagnostic of IPF. BAL cell count does not clearly differentiate between fibrotic non-specific interstitial pneumonia and IPF either diagnostically or prognostically. BAL in IPF should be considered in all patients with suspected infection, malignancy or acute exacerbations. In such cases, it may be diagnostic. Because of few and conflicting results BAL fluid analysis has very little clinical relevance determining prognosis and response to treatment in IPF.

Bronchoalveolar lavage

Pulmonary diseases have traditionally been evaluated by clinical data, laboratory tests, lung function tests, imaging procedures and tissue biopsies. Bronchoalveolar lavage (BAL), performed during fiberoptic bronchoscopy, is a useful adjunct to lung biopsy in the diagnosis of nonneoplastic lung diseases in a limited number of settings. There are no absolute contraindications to the performance of BAL beyond those commonly associated with bronchoscopy. BAL is able to provide cells and solutes from the lower respiratory tract and may provide important information about diagnosis and yield insights into immunologic, inflammatory, and infectious processes taking place at the alveolar level.[1] BAL, when combined with clinical data and high-resolution computed tomography of the chest, can facilitate the diagnosis of various diffuse lung diseases. BAL is an excellent method of obtaining specimens to rule out malignancy and infections, particularly opportunistic infections in immunocompromised hosts by pathogenic organisms not known to colonize the lower respiratory tract.[1] Examination of BAL cells or acellular components of BAL via gene microarray technology or proteomic analyses may allow BAL to assume a more prominent role in diagnosis and management of lung disease in the near future.

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial lung disease of unknown etiology characterized by progressive dyspnea, reduced lung volumes, impaired

* Correspondence to: Alberto Pesci, Clinica Pneumologica, Azienda Ospedaliera San Gerardo di Monza, Via Pergolesi 33, 20052 Monza, Italy. Fax: + 39 2339437.
E-mail address: alberto.pesci@unimib.it (A. Pesci).

0954-6111/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2010.03.019

gas exchange, and the histopathologic signature of usual interstitial pneumonia (UIP). IPF is included in idiopathic interstitial pneumonia (IIP). The disease follows a relentlessly course. Mean survival time from the diagnosis is 2.5–3.5 years. In the event of rapid worsening of the patient's condition, the differential diagnosis between an acute exacerbation and complications is vital. Because of its poor prognosis and no established effective therapy, the differential diagnosis of IPF from other IIP is important.[2]

Bronchoalveolar lavage in idiopathic pulmonary fibrosis

BAL is a milestone in IPF respiratory research

It is beyond the scope of this text to address IPF pathogenesis in any detailed fashion as this has been done in other major references[2] so only a few comments will be made here. Bronchoalveolar lavage has been enormously helpful in elucidating the key immune effector cells driving the inflammatory response in IPF.[1] Increase in polymorphonuclear leukocytes, neutrophil products, eosinophils, eosinophil products, activated alveolar macrophages, alveolar macrophage products, cytokines, chemokines, growth factors for fibroblasts, and immune complexes have been noted in BAL of patients with IPF.[1] Because components retrieved in BAL fluid are in close proximity to diseased tissue the study of cells and proteinaceous substances in BAL continues to provide insight into the pathogenesis and host immunity responses involved in inflammation, fibrosis, and acute injury.

BAL for diagnosis of IPF

In the patients suspected to have UIP, the pattern of inflammatory cells identified may be helpful in narrowing the differential diagnosis of fibrosing interstitial pneumonias but is not diagnostic of IPF. The BAL fluid analysis in IPF typically shows an increase in total cell count, polymorphonucleated neutrophils (>5%), and eosinophils (>2%).[1,2] These data were confirmed in studies conducted after the recent classification[3–7] (Table 1).

Table 1 Bronchoalveolar lavage cell counts in idiopathic pulmonary fibrosis.

Source	No of patients	Cell/ml × 10^5	Ly %	Neu %	Eo %
Welker L et al., 2004[3]	112	3.4	11.0	6.0	2.0
Kinder BW et al., 2008[4]	156	nd	8.0	6.0	2.0
Veeraraghavan S et al., 2003[5]	35	2.4	4.0	9.0	7.0
Tabuena RP et al., 2005[6]	81	1.74	3.2	1.0	0.4
Ryu YJ et al., 2006[7]	67	nd	5.5	7.0	nd
X mean	451	2.51	6.34	5.8	2.85

Ly = lymphocytes; Neu = neutrophils; Eo = eosinophils.

It has been shown that there is no correlation between the percentage of various cell types found in BAL of IPF patients and various clinical parameters, serum tests, or pulmonary function studies.[8] This pattern, however, is much the same as most idiopathic interstitial pneumonias or other fibrosing lung conditions. In IIPs an increase in BAL neutrophils (levels >5%) is noted in 70–90% of patients. The presence of a BAL neutrophilia increases the likelihood of an underlying fibrosing process (IPF, fibrosing alveolitis of rheumatological disease, asbestosis, or fibrotic sarcoidosis), the proportions of neutrophils correspond to the extent of reticular change on HRCT.[9] BAL eosinophilia may also be mild or moderate. An associated increase in BAL eosinophils (levels >2%) is apparent in 40–60% of IPF patients.[10] When eosinophils represent more than 20% of the count, consideration should be given to an eosinophilic lung disease.[11] An increase in BAL lymphocytes is noted in 10–20% of IPF patients. Lymphocytosis is not a feature of UIP, and counts above 15% should alert to an alternative diagnosis such as NSIP, cryptogenic organizing pneumonia, hypersensitivity pneumonitis, sarcoidosis, drug-induced lung disease or other granulomatous lung disease.[1,12] In a recent study Ohshimo S et al. showed that BAL lymphocytosis (>30%) changed diagnostic perception in six of 74 patients who would have been misdiagnosed as having IPF without BAL.[13] This study demonstrates that the addition of BAL to the diagnostic procedures is useful in patients suspected of having IPF with a confident CT diagnosis and consistent clinical features, in the absence of a surgical biopsy. BAL cell differentials are of additional diagnostic benefit in this clinical setting.

BAL and/or transbronchial biopsy were considered requirements for the exclusion of other diseases in a patient with IPF who did not undergo surgical lung biopsy as one of the four major criteria for making a clinical diagnosis of IPF according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) IPF Statement of 2000. In the ATS/ERS international consensus classification of idiopathic interstitial pneumonias (IIPs) of 2002,[2] BAL analysis was no more found to be important in the diagnostic work-up of IPF. In that statement, a confident CT diagnosis of IPF with consistent clinical features was considered to be sufficient to make an accurate diagnosis of IPF without surgical biopsy.

Key points

- A finding of raised neutrophils (>5%) and raised eosinophils (>2%) is characteristic of IPF, but not diagnostic
- BAL is not required as a diagnostic tool in patients with clinical features and HRTC appearances typical of IPF
- In IPF a lone increase in BAL lymphocytes or eosinophils is uncommon and these observations may influence diagnostic confidence

BAL in differential diagnosis and Co morbidity of IPF

BAL is a non-invasive diagnostic procedure in interstitial lung diseases (ILD), not only for the diagnosis of certain

non-IIP diseases such as hypersensitivity pneumonitis, sarcoidosis, histiocytosis x or pulmonary alveolar proteinosis but also for the exclusion of infection or malignancy.[1] In addition, the pattern of inflammatory cells identified may be helpful in narrowing the differential diagnosis of fibrosing interstitial pneumonias. When pulmonary infiltrates are associated with immunosuppressive therapy, BAL makes a crucial contribution to the detection of opportunistic infection superimposed to lung fibrosis. Acute exacerbations of IPF are dramatic scenario characterized by diffuse alveolar damage (DAD) superimposed on UIP. In this condition the use of BAL may be contribute to the diagnosis showing a pattern confident with DAD: no evidence of pulmonary infection; neutrophilia (>50%); presence of reactive type II pneumocytes.[14–16]

The differentiation between fibrotic NSIP and UIP, in absence of surgical lung biopsy, is a difficult challenge for physicians. After the first description of NSIP in 1994, BAL lymphocytosis is more likely suggestive of NSIP rather than UIP.[1,2] A few recent studies have also shown that BAL could provide substantial diagnostic information on UIP and NSIP.[1] A retrospective study was undertaken by Ryu et al.[7] with fibrotic IIP (UIP 87/NSIP 35). They concluded that BAL is an useful non-invasive tool in fibrotic IIP, not only for excluding a variety of specific non-IIP diseases but also for narrowing the differential diagnosis and predicting the prognosis in the absence of an histopathologic diagnosis. Particularly BAL lymphocytosis was more frequently observed in NSIP than UIP while the absence of BAL lymphocytosis suggested a diagnosis of UIP. The presence of BAL neutrophilia, however, could not predict a diagnosis of IPF. These results contrasted with the report by Veeraraghavan et al.[5] which concluded that the BAL findings in 54 patients with a clinical diagnosis of UIP had no diagnostic role in discriminating between UIP and NSIP. Also Daniil et al.[17] did not find a BAL lymphocytosis in a small cohort of NSIP patients. BAL findings were compared between UIP and fibrotic NSIP in a large cohort of patients presenting with the clinical features of IPF. Welker et al[3] in a large study which aim was to quantify how the like hood for a given diagnosis changes with the knowledge of BAL cell differentials, concluded that BAL do not discriminate between UIP and NSIP in patients presenting with clinical features of UIP and have no prognostic value, once the distinction between the two has been made histologically. These data suggest that BAL differential cell count per se provide substantial diagnostic information only in relatively frequent diseases, such as sarcoidosis and UIP and are less helpful in infrequent diseases (NSIP, etc.). Therefore the role of BAL in fibrotic IIP is still controversial.

Key points

- In patient with uncertain diagnosis, typical BAL cellular profiles may allow a diagnosis of hypersensitivity pneumonia, pulmonary histiocytosis x, occupational dust exposure, or sarcoidosis
- BAL in IPF should be considered in all patients with suspected infection, malignancy or acute exacerbations. In such cases, BAL may be diagnostic
- The BAL cell count does not clearly differentiate between fibrotic NSIP and UIP
- An increase in BAL lymphocytes is in favour of NSIP (idiopathic or secondary)

BAL in prognosis and follow up of IPF

In the follow-up depicting prognosis and response to treatment BAL fluid analysis has less clinical relevance. There have been conflicting results in previous studies evaluating the relationship between BAL fluid cellularity and outcome.

In studies performed in IPF, prior to the recent reclassification,[2] it was demonstrated that higher BAL fluid neutrophilia and/or eosinophilia predicted a subsequent deterioration in pulmonary function test result parameters or a poor response to therapy, whereas BAL fluid lymphocytosis was associated with responsiveness to therapy and better prognosis.[18–23] However, these relationships are too inconsistent in individual patients for BAL to be used as a reliable prognostic guide and, in addition, all these studies were performed in IPF patients without firm diagnostic criteria. In more recent study, Veeraraghavan et al.[5] reported that BAL had neither diagnostic role nor prognostic value in 54 patients with either IPF or idiopathic NSIP. In a retrospective study Ryu et al.[7] evaluated whether the BAL findings could predict the prognosis in the absence of the histological diagnosis. They concluded that BAL is an useful non-invasive tool in fibrotic IIP, not only for excluding a variety of specific non-IIP diseases but also for narrowing the differential diagnosis and predicting the prognosis in the absence of an histopathologic diagnosis. In particular, the presence or absence of BAL lymphocytosis was important, unless pathologic diagnosis was confirmed, it can be an independent predictor of good prognosis in fibrotic IIP. BAL neutrophilia, however, did not have prognostic value in this study. In another study of 81 IPF patients, BAL fluid neutrophil and lymphocyte counts predicted mortality in current smokers, but not among never smokers or former smokers.[6] A study of a large well characterized cohort of IPF patients with comprehensive and long-term follow-up showed that an increase in BAL fluid neutrophil percentage was an independent predictor of early mortality.[4] This study found no significant interaction with smoking on the association of BAL fluid neutrophil percentage and mortality. Selman M et al[24] evaluated the clinical behaviour and survival rate of IPF patients classified as "'rapid" or "'slow" progressors according to the duration of symptoms before diagnosis. IPF rapid progressors did not have more BAL neutrophils and or eosinophils than slow progressor, however, BAL from rapid progressors showed a 2-fold increase of active matrix metalloproteinase-9, and induced a higher fibroblast migration compared with slow progressors and controls.

The value of serial BAL is limited, although it has been incompletely studied. In one observational study of 32 patients followed with serial BAL for a median of four years, patients with definite and sustained clinical improvement had a reduction in serial lavage total cell counts toward the normal range.[25]

Key points

- Because of few and conflicting results BAL fluid analysis has very little clinical relevance determining prognosis and response to treatment in IPF
- The number and type of cells found in the BAL fluid have no prognostic value and therefore serial BAL for monitoring the disease progression or response to treatment are not advised.

Conclusions

BAL is not always required in the assessment of IPF. However, if, as is commonly the case, it has been performed in diagnostic work-up of diffuse parenchymal lung disease to exclude infection or tumor, the result may assist in the decision to perform a surgical biopsy and in distinguishing different form of IIP. Although not diagnostic in IIP, a "typical" BAL cell pattern strengthens the clinical diagnosis and may contribute to the clinico-radiologic-pathologic assessment in difficult cases. Even if the clinical utility of BAL in IPF should be reconsidered, further studies are needed to define the clinical utility of this procedure in this intriguing disease.

Conflict of interest

All authors do not have any conflict of interest.

Copyright

All the authors have seen and approved the paper and the work has not been, and will not be, published elsewhere.

Authorship

All Authors made substantial contributions to the conception and design of the paper, drafting the article and revising it.

References

1. Costabel U, Guzman J. Bronchoalveolar lavage in interstitial lung disease. *Curr Opin Pulm Med* 2001;**7**:255–61.
2. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;**165**:277–304.
3. Welker L, Jorres RA, Costabel U, Magnussen H. Predictive value of BAL cell differentials in the diagnosis of interstitial lung diseases. *Eur Respir J* 2004;**24**:1000–6.
4. Kinder BW, Brown KK, Schwarz MI, et al. Baseline BAL neutrophilia predicts early mortality in idiopathic pulmonary fibrosis. *Chest* 2008;**133**:226–32.
5. Veeraraghavan S, Latsi PI, Wells AU, et al. BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. *Eur Respir J* 2003;**22**:239–44.
6. Tabuena RP, Nagai S, Tsutsumi T, et al. Cell profiles of bronchoalveolar lavage fluid as prognosticators of idiopathic pulmonary fibrosis/usual interstitial pneumonia among Japanese patients. *Respiration* 2005;**72**:490–8.
7. Ryu YJ, Chung MP, Han J, et al. Bronchoalveolar lavage in fibrotic idiopathic interstitial pneumonias. *Respir Med* 2007;**101**:655–60.
8. Crystal RG, Gadek JE, Ferrans VJ, et al. Interstitial lung disease: current concepts of pathogenesis, staging and therapy. *Am J Med* 1981;**70**:542–68.
9. Wells AU, Hansell DM, Rubens MB, et al. Fibrosing alveolitis in systemic sclerosis. Bronchoalveolar lavage findings in relation to computed tomographic appearance. *Am J Respir Crit Care Med* 1994;**150**:462–8.
10. Cushley MJ, Davison A, du Bois RM, Egan J, Flower CD, Gibson GJ, Greening AP, Ibrahim NB, Johnston ID, Mitchell DM, et al. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. *Thorax* 1999;**54**:S1–S30.
11. Allen JN, Davis WB. Eosinophilic lung diseases. *Am J Respir Crit Care Med* 1994;**150**:1423–38.
12. Nagai S, Handa T, Ito Y, Takeuchi M, Izumi T. Bronchoalveolar lavage in idiopathic interstitial lung diseases. *Semin Respir Crit Care Med* 2007;**28**:496–503.
13. Ohshimo S, Bonella F, Cui A, et al. Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009;**179**:1043–7.
14. Grotte D, Stanley MW, Swanson PE, Henry-Stanley MJ, Davies S. Reactive type II pneumocytes in bronchoalveolar lavage fluid from adult respiratory distress syndrome can be mistaken for cells of adenocarcinoma. *Diagn Cytopathol* 1990;**6**:317–22.
15. Biyoudi-Vouenze R, Tazi A, Hance AJ, Chastre J, et al. Abnormal epithelial cells recovered by bronchoalveolar lavage: are they malignant? *Am Rev Respir Dis* 1990;**142**:686–90.
16. Nakos G, Kitsiouli EI, Tsangaris I, Lekka ME, et al. Bronchoalveolar lavage fluid characteristics of early intermediate and late phases of ARDS. Alterations in leukocytes, proteins, PAF and surfactant components. *Intensive Care Med* 1998;**24**:296–303.
17. Daniil ZD, Gilchrist FC, Nicholson AG, et al. A histologic pattern of nonspecific interstitial pneumonia is associated with a better prognosis than usual interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 1999;**160**:899–905.
18. Haslam PL, Turton CW, Lukoszek A, et al. Bronchoalveolar lavage fluid cell counts in cryptogenic fibrosing alveolitis and their relation to therapy. *Thorax* 1980;**35**:328–39.
19. Rudd RM, Haslam PL, Turner-Warwick M. Cryptogenic fibrosing alveolitis. Relationships of pulmonary physiology and bronchoalveolar lavage to response to treatment and prognosis. *Am Rev Respir Dis* 1981;**124**:1–8.
20. Watters LC, Schwarz MI, Cherniack RM, et al. Idiopathic pulmonary fibrosis: pretreatment bronchoalveolar lavage cellular constituents and their relationships with lung histopathology and clinical response to therapy. *Am Rev Respir Dis* 1987;**135**:696–704.
21. Schwartz DA, Helmers RA, Galvin JR, et al. Determinants of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1994;**149**:450–4.
22. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European respiratory Society (ERS). *Am J Respir Crit Care Med* 2000;**161**:646–64.
23. Matsuo K, Tada S, Shibayama T, et al. Factors affecting prognosis of idiopathic interstitial pneumonia. *Acta Med Okayama* 1996;**50**:37–46.
24. Selman M, Carrillo G, Estrada A, et al. Accelerated variant of idiopathic pulmonary fibrosis: clinical behavior and gene expression pattern. *PLoS One* 2007;**2**:e482.
25. Turner Warwick M, Haslam PL. The value of serial bronchoalveolar lavages in assessing the clinical progress of patients with cryptogenic fibrosing alveolitis. *Am Rev Respir Dis* 1987;**135**:26.